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REVIEW

Limiting the morbidity of inguinofemoral lymphadenectomy in vulvar cancer patients; a review

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ABSTRACT

Introduction: Inguinofemoral lymphadenectomy (IFL) is performed in the treatment for vulvar cancer. One or more complications after IFL is reported in up to 85% of the patients. This review presents an overview of surgical techniques and peri- and post-operative care that has been studied in order to reduce the morbidity associated with IFL in vulvar cancer patients.

Areas covered: Current knowledge on post-operative complications after different surgical techniques and peri- and post-operative protocols were discussed. A systematic literature review was conducted using MEDLINE, EMBASE and the Cochrane library on 20 February 2017. In order to be eligible for inclusion, studies must report the associated post-operative morbidity per surgical technique, or peri- or post-operative care given after IFL in vulvar cancer patients.

Expert commentary: After the implementation of several new surgical techniques, the morbidity after IFL decreased but remains high and clinically meaningful. More research is needed on surgical techniques and peri-or post-operative care to further reduce the complication rates after IFL in vulvar cancer patients.

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Inguinofemoral lymphadenectomy; lymph node excision; morbidity; postoperative complications; vulvar cancer; vulvar neoplasm

1. Introduction

Vulvar cancer is the fourth most common gynecologic cancer after endometrial, ovarian, and cervical cancer. Vulvar cancer is a rare disease with an incidence of 2.4 per 100,000 women [1]. Over the past few decades, the incidence of vulvar cancer increased [2]. Vulvar cancer mostly affects elderly women, with more than half of the patients being above the age of 70 years at the time of diagnosis. The most common histological type of vulvar cancer is squamous cell carcinoma (SCC), which accounts for over 80% of the cases [3].

The dissemination of vulvar SCC may occur by three different routes: direct extension, lymphogenic spread, and hematogenic spread. The initial spread occurs usually to the inguinofemoral lymph nodes. As soon as the depth of infiltration is more than 1 mm, inguinofemoral lymph node metastases can already be present. Therefore, evaluation of inguinofemoral lymph nodes is crucial. The cornerstone in the treatment of primary vulvar SCC is surgery, consisting of both local tumor resection and inguinofemoral lymph node staging and/or dissection. The treatment for vulvar cancer has developed throughout the last decades. For years, radical vulvectomy with 'en bloc' bilateral inguinofemoral lymphadenectomy was a well-established treatment. In the last three decades, less radical surgery was introduced to decrease morbidity with comparable or improved prognosis. Nowadays, the standard treatment of early stage vulvar SCC consists of radical local excision of the tumor combined with a sentinel node (SN) procedure and/or inguinofemoral lymphadenectomy (IFL). The SN procedure is safe to perform instead of an IFL in patients with a unifocal tumor <4 cm without suspicious lymph nodes in the groins [4]. In patients with a larger tumor, multifocal disease and/or a positive SN and in patients with local recurrent disease without earlier IFL, an IFL is indicated. After the implementation of the SN, in approximately half of the patients with vulvar SCC an IFL is still indicated [5].

Unfortunately, IFL is associated with significant short- and long-term complications. The occurrence of one or more groin wound complications is reported in 66–85% of the patients [6,7]. Wound breakdown, wound infection, lymphoceles, lymphedema, cellulitis, and erysipelas are the most reported complications. Because IFL will always have a place in the treatment of vulvar cancer, it is important to look for adjustments, which may reduce the associated morbidity.

The aim of this review is to create an up-to-date summary of surgical techniques and peri- and postoperative care that have been performed to reduce the morbidity of IFL in vulvar cancer patients.

2. Methods

2.1. Literature search

We performed a systematic search of the literature on 20 February 2016 using MEDLINE, EMBASE, and the Cochrane library. The following search (MeSH)terms and synonyms

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were used for 'lymphadenectomy' combined with 'vulvar cancer' (lymphadenectomy, inguinofemoral lymphadenectomy, groin surgery, groin dissection, lymph node dissection, lymph node surgery, lymph node excision; vulvar cancer, vulvar tumor, vulvar carcinoma, vulvar neoplasm, vulvar squamous cell carcinoma). The search was restricted to the English and Dutch language.

2.2. Study selection

In order for an article to be eligible, the following predefined criteria had to be met [1]: (randomized) (un)controlled trial; controlled or uncontrolled prospective or retrospective study [2]; IFL for vulvar cancer patients aged >18 years; and [3] report the associated complication rate per studied surgical technique or peri- or postoperative care.

2.3. Outcome measures

Our primary outcomes of interest were

- Complication rate per surgical technique and/or peri-, or postoperative care
  - Short-term complications <8 weeks after surgery
    - Wound breakdown
    - Wound infection
    - Lymphocele
  - Long-term complications >8 weeks surgery
    - Cellulitis or erysipelas (recurrent)
    - Lower extremity lymphedema

Secondary outcome of interest was

- Quality of life

2.4. Data extraction and analysis

Relevant data on study population, study design, surgical technique, peri-or postoperative protocol, and the complication rates were extracted from the included studies. Similar complications were grouped together such as seroma and lymphocele, cellulitis and erysipelas, wound dehiscence and wound breakdown.

Quality of the included studies was categorized according to the levels for intervention studies of evidence of the Oxford Centre of Evidence Based Medicine [8]. Level one evidence included a systematic review of randomized controlled trials (RCT), level two evidence included a randomized trial, level three, a non-RCT, level four, case-series, case-control studies, or historically controlled studies.

The aim of this review was to create an up-to-date summary of all available evidence regarding surgical techniques and peri- and postoperative care protocols after IFL in vulvar cancer patients. Therefore, we included all published articles concerning this subject. As both controlled and uncontrolled trials were expected to include in this review, we planned not to perform meta-analyses.

3. Results

3.1. Literature search

The search yielded a total of 1988 articles, and after removal of duplicates, 1363. One author (AP) screened all titles and checked for relevant abstracts; 123 abstracts were found to be relevant and were retrieved in full text. The same author assessed the articles for eligibility using the predefined criteria as stated in our methods. A total of 36 studies were included in this review.

3.2. Study characteristics

The research designs of the included studies were mainly retrospective (23 studies), six were prospective uncontrolled studies, five RCTs, and two prospective controlled studies. Study populations ranged between 5 and 194 patients and were studied in the period from 1955 until 2016. The quality of the included studies was mainly level four evidence (31 studies). Two included RCTs were downgraded to level three evidence because they did not perform a sample size calculation and both included less than 15 patients [9,10] (See Table 1).

The following surgical interventions were studied: separate incisions or radical vulvectomy with 'en bloc' lymphadenectomy, unilateral IFL, sparing of saphenous vein, Sartorius transposition, dura mater for femoral vessel coverage, minimally invasive technique, preservation of fascia lata, harmonic scalpel or electrosurgery, plasmajet, VH fibrin sealant, lymphatic microsurgical venous anastomosis (LYMPHA technique), lymphatic flap, method of skin closure, anticoagulation, postoperative drainage and compression garments. None of the included studies reported data on quality of life. For an overview of the association of the above-described interventions on postoperative morbidity after IFL, see Table 2.

3.3. Modifications of surgery

3.3.1. Type of groin incision

The morbidity of IFL by type of groin incision was reported by ten included studies; both separate incisions and the 'en bloc' approach were described. See Table 3.

Only two retrospective studies studied postoperative complications after IFL by separate incisions versus the 'en bloc' approach [14,15]. Helm et al. [14] did report a reduction of patients with wound breakdown using separate incisions but this reduction was not statistically significant. The second study described a reduction of the wound breakdown rate and an increase in lymphoceles after using separate incisions, but did not perform any statistical tests [15]. Six other studies report the incidence of postoperative complications after the use of separate incisions without a control group. Overall, it can be concluded that the occurrence of wound breakdown, lymphedema, and cellulitis/erysipelas was reduced by using separate incisions with an increase in lymphoceles.

To determine further reduction of the morbidity associated by IFL using separate incisions, Manci et al. [30] compared skin

Table 1. Characteristics of included studies.

Study	Year	Design	Patients	Intervention	Control	Level of evidence
Hacker 1981 [11]	1957–1978	Retrospective	100	Separate incisions	*	4
Piver 1983 [12]	1957–1971	Retrospective	115	Sodium warafin, dextran, none	Heparine	4
Podratz 1983 [7]	1955–1975	Retrospective	175	'en bloc' approach		4
Fiorica 1991 [13]	1987–1990	Prospective	20	Cadaver dura mater	*	4
Helm 1992 [14]	1969–1988	Retrospective	64	Separate incisions	'en bloc' approach	4
Lin 1992 [15]	1970–1988	Retrospective	82	Separate incisions	'en bloc' approach	4
Finan 1994 [16]	1991–1992	Prospective	11	Artificial dura film	*	4
Burke 1995 [17]	1978–1994	Retrospective	76	Bilateral and/or unilateral IFL	*	4
Paley 1997[18]	1975–1994	Retrospective	101	Sartorius transposition	Not Sartorius transposition	4
Bell 2000 [19]	1990–1998	Retrospective	60	Preservation of the fascia lata	*	4
Zhang 2000 [20]	1990–1998	Retrospective	83	Preservation saphenous vein	Ligation saphenous vein	4
Gould 2001 [21]	1992–1999	Retrospective	67	Separate incisions	*	4
Gori 2002 [22]	1992–1997	Retrospective	45	Unilateral IFL	Bilateral IFL	4
Gaarenstroom 2003 [6]	1993–2000	Retrospective	101	Separate incisions	*	4
Rouzier 2003 [23]	1978–2000	Retrospective	194	Sartorius transposition Preservation of saphenous vein	Not Sartorius transposition Ligation saphenous vein	4
Judson 2004 [24]	1996–2002	RCT	61	Sartorius transposition	Not Sartorius transposition	2
Micheletti 2005 [25]	1981–2002	Retrospective	156	Preservation fascia lata	*	4
Dardarian 2006 [26]	1992–2003	Retrospective	29	Sparing saphenous vein	Ligation saphenous vein	4
Zhang 2007 [27]	1989–2005	Retrospective	64	Preservation saphenous vein	Ligation saphenous vein	4
Carlson 2008 [28]	2002–2005	RCT	137	VH fibrin sealant	No VH sealant	2
Pellegrino 2008 [29]	2005–2007	Retrospective	42	Harmonic scalpel	Conventional electrosurgery	4
Van der Zee 2008 [4]	2000–2006	Prospective	457	Separate incisions	*	4
Manci 2009 [30]	2000–2007	RCT	62	Inferior skin incision	Superior skin incision	2
Sawan 2009 [10]	2006	RCT	14	Prophylactic compression garments	Not prophylactic compression garments	3
Hinten 2011 [5]	1988–2009	Retrospective	164	'en bloc' approach and separate incisions	*	4
Madhuri 2011 † [9]	Not reported	RCT	18	Plasmajet	Not plasmajet	3
Walker 2011 [31]	2001–2009	Retrospective	50	Continuous subcuticular suture	Staples	4
			56	Separate incisions	*	
				Length of drainage	*	
Xu 2011 [32]	2008–2010	Retrospective	17	VEIL abdominal approach	*	4
Li 2012 [33]	2004–2009	Retrospective	24	Modified triple incisions	*	4
Soliman 2012 [34]	2002–2009	Retrospective	34	Separate incisions	*	4
Morotti 2013 [35]	2009–2011	Prospective	15	LYMPHA	No LYMPHA (historical cohort)	4
Li 2015 [36]	2007–2013	Prospective	58	Sartorius tendon transposition	Sartorius transposition	4
Wang 2015 [37]	2010–2013	Prospective	21	VEIL hypogastric subcutaneous approach	*	4
Gentileschi 2016 [38]	Not reported	Prospective	5	Lymphatic flap	No lymphatic flap	4
Wu 2016 [39]	2011–2016	Prospective	37	VEIL lateral approach	*	4
Jain 2017 [40]	2011–2015	Retrospective	12	R-VEIL	*	4

†: conference abstract, *: not studied, IFL: inguinofemoral lymphadenectomy, VEIL: video endoscopic lymphadenectomy, LYMPHA: lymphatic microsurgical preventive healing approach, R-VEIL: robot-assisted video endoscopic inguinal lymphadenectomy.

access above or below the inguinal ligament in a RCT and found an advantage for incision above the ligament; wound dehiscence in 32% versus 17%, lymphocele in 19% versus 6%, respectively, although there was no statistically significant difference.

3.3.2. Laterality of IFL

Unilateral IFL as an alternative to bilateral IFL was studied in a selected group of patients with lateralized tumors (tumor with medial margin >1 cm from the midline) without palpable groin lymph nodes. Two studies reported less complications in unilaterally treated patients [17,22]. The number of patients with wound dehiscence or lymphedema is significantly reduced by performing a unilateral IFL from 24% to 0% and 67% to 8%, respectively ($p < 0.001$) [22]. In conclusion, unilateral IFL does reduce morbidity but can only safely be performed in patients with early stage and lateralized vulvar cancer [17].

3.3.3. Sparing of the saphenous vein

The classic description of IFL includes ligation of the saphenous vein. It was suggested that sparing the saphenous vein might reduce the complications associated with IFL. Four retrospective studies reported the complication rates after sparing versus ligation of the saphenous vein [20,23,26,27]. See Table 4 for an overview of the outcomes of these studies. There was a significant lower number of groins with wound infection [23,26], wound breakdown [20,23,26], lymphedema [23,26,27], and cellulitis/erysipelas [20,27] after sparing of the saphenous vein. There was no evidence of effect for the reduction of lymphoceles. It can be concluded that sparing of the saphenous vein reduces the postoperative wound complications after IFL.

3.3.4. Coverage of femoral vessels

The transposition of the Sartorius was first introduced by Way as modification to protect the femoral vessels in case of

Table 2. Influence of intervention on the complication rate after IFL per level of evidence.

Level of evidence	Decrease	Increase	No association	Unclear
Level 1	None	None	None	None
Level 2	None	Fibrin sealant	Sartorius transposition Skin access above or below the inguinal ligament	None
Level 3	None	None	None	Plasmajet Prophylactic compression garment
Level 4	Separate incisions Unilateral IFL Sparing saphenous vein Preservation fascia lata LYMPHA* Continuous suture	'en bloc' approach Bilateral IFL Artificial dura mater	Cadaver dura mater	(R-)VEIL Harmonic scalpel or electrosurgery Anticoagulation Duration of drainage Lymphatic flap

*: only lymphedema studied; (R-) VEIL: (robot-assisted) video endoscopic inguinofemoral lymphadenectomy; IFL: inguinofemoral lymphadenectomy; LYMPHA: lymphatic microsurgical preventive healing approach.

Table 3. Separate incisions versus 'en block' resection for inguinofemoral lymphadenectomy; complications in percentages.

		Short term									Long term						
		Wound infection			Wound breakdown			Lymphocele			Lymphedema			Cellulitis/erysipelas			
Study	*N*	Separate	En bloc	*p*-Value	Separate	En bloc	*p*-Value	Separate	En block	*p*-Value	Separate	En bloc	*p*-Value	Separate	En bloc	*p*-Value	Overall ≥1 complication
'en bloc' versus separate incisions per patient																	
Helm 1992	64	-	-		19	34	NS	31	19	NS	—	—		22	16	NS	--
Lin 1992	82	-	—		22	53	—	15	0	--	15	13	--	—	—	--	--
'en bloc' per patient																	
Podratz 1983	175		85†			85†			11				69			13	--
Separate incisions per patient																	
Gaarenstroom 2003	101	39			17			40			28				—		66
Gould 2001	67	35			19			13			30				22		--
Hacker 1981	100	9			44			13			20				2		--
Hinten 2011††	164	29			19			29			49				34		--
Van der Zee 2008 ‡	166	21			34			--			25				16		--
Separate incisions per groin																	
Gaarenstroom 2003	187	27			11			27			21				—		52
Soliman 2012	64	3			10			13			5				24		--

NS: not significant.

†: including wound infection, wound breakdown and necrosis; ††: both en bloc and separate incisions, ‡: sentinel node procedure with subsequent inguinofemoral lymphadenectomy.

Table 4. Sparing versus ligation of the saphenous vein; complications in percentages.

		Short term						Long term									
		Wound infection			Wound breakdown			Lymphocele			Lymphedema			Cellulitis/erysipelas			
Study	*N*	Sparing	Ligation	P-value	Sparing	Ligation	P-value	Sparing	Ligation	P-value	Sparing	Ligation	P-value	Sparing	Ligation	P-value	Overall ≥1 complication
Per groin																	
Dardarian 2006	49	0	45	<0.001	0	25	<0.02	0	0	–	11	39	<0.05	0	6	NS	–
Rouzier 2003	355	18	30	0.01	16	36	<0.001	–	–		23	45	<0.001	–	–		–
Zhang 2000	139	–	–		13	38	0.001	10	4	NS	32	70	–	18	39	0.006	–
Zhang 2007	128	68	73	NS	–	–		26	32	NS	25	48	<0.01	21	41	<0.05	–

NS: not significant.

wound breakdown and to decrease the morbidity after IFL [41]. The effect of transposition of the Sartorius on the complication rate is reported in three studies, one RCT [24] and two retrospective studies [18,23]. Judson et al. [24] randomized for either sartorius transposition or not. They found a statistically significant increase of lymphocele formation in patients in the transposition group. Other outcomes, such as wound breakdown, wound infection, and lymphedema did not differ between those two groups of patients.

One retrospective study reported an increase in patients with lymphedema after transposition of the Sartorius, with statistical significance [23] and another study reported a reduction of wound infections after transposition [18]. These studies did not report significant differences between wound breakdown and lymphocele. See Table 5 for an overview of results.

Another explored surgical technique during IFL to cover the groin vessels is Sartorius tendon transposition versus Sartorius transposition as investigated by one case-control study [36]. Wound breakdown and chronic lymphedema were significantly reduced in the Sartorius tendon transposition group, 30% versus 3.6% (p = 0.012) and 33.3 versus 7.1% respectively (p = 0.022). However, none of the studies report the morbidity after tendon transposition versus no tendon or Sartorius transposition.

In the past, cadaver dura mater was used to cover the groin vessels but this is difficult and more time consuming than Sartorius transposition, besides the risk of transmittance of viral infections [13]. The artificial dura mater was not effective and increased the complications after IFL [16].

In conclusion, there is no evidence that covering the femoral vessels by transposition of the Sartorius or cadaver or artificial dura mater does reduce the complications after IFL in vulvar cancer patients.

3.3.5. Minimally invasive IFL

In the previous years, minimally invasive techniques were developed for IFL to reduce the postoperative complications. After the introduction in other malignancies such as penile cancer and melanoma, video endoscopic IFL (VEIL) was studied in vulvar cancer patients. Until now, there is limited English literature on vulvar cancer. Four studies concerning VEIL in vulvar cancer patients were included in this review [32,37,39,40]. These studies were published between 2011 and 2017, two were prospective and two retrospective. In total, 87 patients were included (75 patients from China and 12 patients from India). For results see Table 6.

Xu et al. used the abdominal approach for VEIL and reported no inguinal wound-related complications besides one patient with exhibited lymphorrhea through the drain orifice [32]. The second study used a hypogastric subcutaneous approach and reported only one patient with a lymphocele (5%); furthermore, no other inguinal wound complications were observed [37]. The third study used a 3-incision lateral approach to perform VEIL in 37 patients and was the largest published study in vulvar cancer patients. They described wound breakdown in 3% of the patients; no other complications such as wound infection, lymphocele, lymphedema, and cellulitis were reported in these patients [39]. The last study performed in India used robot-assisted VEIL (R-VEIL)

Table 5. Transposition of Sartorius versus not Sartorius transposition, complications in percentages.

		Short term								Long term						
		Wound infection			Wound breakdown			Lymphocele			Lymphedema			Cellulitis/erysipelas			
Study	*N*	Sartorius transposition	Not Sartorius transposition	*p*-Value	Sartorius transposition	Not Sartorius transposition	*p*-Value	Sartorius transposition	Not Sartorius transposition	*p*-Value	Sartorius transposition	Not Sartorius transposition	*p*-Value	Sartorius transposition	Not Sartorius transposition	*p*-Value	Overall ≥1 complication
Per patient																	
Judson 2004	61	29	30	–	11	9	–	40	15	0.04	18	33	NS	–	–		–
Paley 1997	101	30	58	0.011				16	18	–	24	26	–				–
Per groin																	
Rouzier 2003	206	28	30	NS	43	36	NS	–	–		55	22	< 0.001	–	–		–

NS: not significant.

to perform IFL. Reported overall complication rate was 75% per patient and 60% per groin [40]. These overall complication rates reported after R-VEIL were even higher to those reported after open IFL by Gaarenstroom et al. of 66% per patient and 52% per groin, respectively [6]. Furthermore, it is unclear if (R-)VEIL is safe in vulvar cancer patients, given a groin recurrence rate as high as 6% in patients using VEIL [39] comparing to 2.5% after using the conventional procedure [42].

In conclusion, (R-)VEIL seems to be feasible for the approach of IFL as described in all studies, but it remains questionable if (R-)VEIL reduces the postoperative complications, and whether this procedure is oncologically safe or not.

3.3.6. Other modifications

More individual studies report modifications on the current surgical techniques of IFL. First of all, the preservation of the fascia lata. Two retrospective studies report after sparing of the fascia lata lower rates of lymphocele, lymphedema, wound infection, and wound breakdown compared to the literature [19,25] and overall short-term complication rate of 38% and long-term complication rate of 14% [25].

The device used during IFL is studied as a possible option to reduce the morbidity. Pellegrino et al. [29] investigated the differences in postoperative complications of using either the harmonic scalpel or conventional electrosurgery. They did not report significant differences between these two groups in the incidence of postoperative complication. In this study, only one patient had a postoperative complication in the harmonic scalpel group (including 22 patients) versus zero patients in the conventional electrosurgery group (including 20 patients). Another study regarding the surgical device used is performed by Madhuri et al. [9] using Plasmajet (a surgery system utilizing kinetic energy and highly controlled thermal effects to seal the tissue). In a conference abstract, they described a pilot RCT in 18 patients and concluded that Plasmajet may reduce the lymphocele formation but did not publish the full paper until now.

Another studied option is the sealing of lymph vessels during IFL, evaluated by Carlson et al. [28] in a RCT. They investigated the addition of VH fibrin sealant sprayed in the groin before sutured closure. Inguinal infections, wound breakdown, lymphoceles, and lymphedema did not significantly differ between the two groups. However, they reported a significant increase in the number of vulvar infections in patients treated by VH fibrin sealant (33% versus 14%, $p = 0.0098$).The overall complication rate for patients treated in the intervention group was 61% versus 59% in the control group. In conclusion, VH fibrin sealant in the groin did not reduce the groin complications after IFL and increased the vulvar wound complications.

The use of lymphatic microsurgical preventive healing approach (LYMPHA) in the prevention of lymphedema during IFL was described by one prospective study in 23 groins [35]. Before incision of the skin, blue dye was injected in the thigh muscles to identify the lymphatic vessels; anatomizes were made between lymphatics from the lower limb and one of the collateral branches of the femoral vein. They reported lymphedema in 8% of the groins after the LYMPHA technique and 36% in the cohort without LYMPHA technique after a mean follow-up of 16.7 (SD 6.2) months. Other groin wound

Table 6. Minimally invasive approach for IFL, complications in percentages.

		Short term			Long term		
Study	*N*	Wound infection	Wound breakdown	Lymphocele	Lymphedema	Cellulitis/erysipelas	Overall ≥1 complication
Per patient							
Xu 2011	17	0	0	0	0	0	0
Wang 2015	21	–	–	5	–	–	–
Wu 2016	37	–	3	0	–	0	–
Jain 2017	12	0	0	33	33	17	75‡
Per groin							
Jain 2017	22	0	0	27	27	9	60‡

‡: including prolonged lymphhorrhea; –: not reported.

complications were not reported. More research is needed before implementation of this technique. Another study used a surgical technique for microsurgical reconstruction of the lymphatic drainage in order to prevent lymphatic drainage impairment. In this study, a lymphatic flap harvested from the flank was used to create a bridge in the gap of lymphatic vessels created by IFL. This technique was used in one groin, while the conventional surgical method was used for the other groin. Patients were evaluated 6 months after surgery, and the limbs treated by the lymphatic flap showed mild edema versus moderate to severe edema in the untreated limb [38].

The method of skin closure was studied by one retrospective study [31]: continuous subcuticular suture was compared to staples. Lymphocele formation was reduced (21% versus 47%, $p = 0.05$) and also a reduction in chronic lymphedema (6% versus 29%, $p = 0.02$) by using subcuticular suture compared to staples. Wound infection and wound breakdown were not influenced by the method of skin closure.

3.4. Modifications of perioperative care

In 1983, one study reported the influence of perioperative prophylactic anticoagulation as a possible cause of lymphocele after IFL. In patients receiving heparin, 42% developed a lymphocele versus 2% in patients receiving sodium warfarin, dextran, or no anticoagulation ($p < 0.01$). The influence of both treatment regimens on the risk of embolism in these patients is unclear. There are no other studies regarding prophylactic anticoagulation and the associated risk of complications after IFL besides this dated publication. Nowadays, the use of heparin is more and more replaced by the use of low-molecular-weight heparin during surgery and postoperative care. No reports about usage of low-molecular-weight heparin are published until now.

The usage of prophylactic intravenous antibiotics is widely accepted during perioperative care, but there were no publications about reducing postoperative (wound) complications.

3.5. Modifications of postoperative care

The postoperative care given might influence the morbidity after IFL. First of all, the postoperative drainage of the groin after IFL might reduce the morbidity. The optimal duration of lymph fluid drainage was studied by only two retrospective studies. Walker et al. [31] reported complications in association with the duration of lymph fluid drainage. The main reason for removal of the drain was production of <50 ml per 24 hours. Wound breakdown and lymphedema were significantly lower in the group of patients drained over 7 days compared to shorter drainage. There was no influence on the number of patients with a wound infection and lymphocele. Another retrospective study showed that higher drain production on the last day *in situ* was associated with an increased risk for any short-term complication but there was no effect found on duration drain *in situ* on the complication rate [5]. Prospective research is needed to determine the optimal duration of postoperative drainage in terms of reduction of complications after IFL.

The second studied modification of postoperative care was the use of prophylactic compression garments by Sawan et al. [10] in 14 patients. Patients were randomly assigned for prophylactic compression garments or best supportive care without compression garments. There was no statistically significant difference in postoperative complication rate regarding wound breakdown, wound infection, lymphocele, and lymphedema. Further (larger) studies are needed to investigate the role of compression garments for reducing the morbidity of IFL.

4. Expert commentary

Where feasible we advise the implementation of separate incisions, unilateral IFL, sparing of the saphenous vein, preservation of the fascia lata, and continuous suture as the standard care for IFL in vulvar cancer patients. These surgical techniques appear to reduce the complication rates. The usage of perioperative fibrin sealant, the 'en bloc' approach, bilateral IFL (for lateralized tumors), and artificial dura mater should not be used as a standard surgical technique for IFL given the higher complication rates. Sartorius transposition, skin access above or below the inguinal ligament, and cadaver dura mater did not influence the complication rate and should not be implemented for IFL. Minimally invasive approach for IFL is promising in terms of reduced of complication rates, but the oncological safety remains unclear. Therefore, minimally invasive techniques for IFL should only be used within the protection of a prospective trial.

Regarding the postoperative care, there is no consensus about optimal drain management and it remains unclear if prophylactic compression garments do reduce the postoperative complication rates. Peri- and postoperative protocols should be studied more extensively before the implementation of new protocols.

Concerning the surgical technique in vulvar cancer patients, the implementation of separate incisions decreased

the morbidity after IFL. A RCT comparing the 'en bloc' approach versus separate incisions investigating the oncologic safety is lacking. However, in a Cochrane review, all observational studies concerning separate incisions were pooled and they concluded that separate incisions were deemed to be oncologically safe [43].

Another surgical technique which appears promising in terms of reduction of postoperative morbidity is minimally invasive IFL. Recently, two reviews were published on this subject [44,45]. One review included ten studies including 236 procedures in 168 patients with penile, vulvar, or vaginal cancer or melanoma. They concluded that the number of wound infections, wound dehiscences, and lymphoceles appeared lower in patients operated by the VEIL technique (overall complication rate 4% of the groins) compared to the open technique [44]. The other systematic review reported an overall complication rate of 13% (lymphocele formation 3.6%, wound infection 1.2%, and lymphedema 0.4%) [45]. This review included nine studies, but only three out of these were published in English. One was included in our review [32], the others were excluded for this review (one study included also vaginal cancer patients and the other did not report data about postoperative complications). So far, no RCTs assessed this new minimally invasive surgical technique. Furthermore, none of the studies included Caucasian women. Moreover, the usage of an ultracision scalpel, which has proven to reduce the incidence of lymphoceles after axillary dissection in breast cancer patients [46], which is used during VEIL and not during the open procedure may partly explain the differences in complication rates. The results on decreasing the incidence of postoperative complications by using the minimally invasive approach are promising, but the oncologic safety of this technique is still unclear. The main concern is the high groin recurrence rate of 6.5% in patients with negative lymph nodes after VEIL [39]. The oncologic safety of pelvic lymph node dissection by laparoscopy is proven for other gynecological malignancies, no differences in number of lymph nodes removed, disease recurrence and survival were reported in several studies [47,48]. A large prospective trial with adequate follow-up of at least 2 years is needed to determine the oncologic safety of VEIL and the postoperative outcomes in Caucasian women with vulvar cancer.

IFL is also performed in patients with a melanoma or penis cancer. In order to reduce bias, in our review only studies including patients with vulva cancer were included. There were several reasons for excluding other indications for IFL than vulvar cancer. First of all, the median age of patients with melanoma is lower than in patients with vulvar cancer; older patients are faced with more comorbidity than younger patients which plays a role in the incidence of postoperative complications. Furthermore, the sex of a patient may influence the complication rate after IFL; therefore, studies on penis cancer, including only men, were excluded from this review. However, more studies on the complications after IFL for melanoma and after axillary dissection for breast cancer are published. Regarding the complications after IFL in melanoma patients, a review included seven studies described different surgical approaches for IFL; applying fibrin sealant in the wound bed, different incision techniques for separate incisions, local versus general anesthesia, early mobilization or postoperative bed rest were studied, but none of these interventions showed a statistically significant reduction in complication rates [49]. A review concerning seroma formation after axillary dissection in breast cancer patients reported a decrease in complications by using ultrasonic scissors, electrotermal bipolar vessel system, suture fixation techniques to reduce the dead space, volume-controlled suction drainage, and active shoulder exercise [50].

There are some limitations to this review. First of all, there is a lack of published studies with level one evidence. As vulvar cancer is a rare disease, it is hard and not realistic to perform a large number of RCTs in vulvar cancer patients. Therefore, this review was mainly based on data from retrospective or observational studies, which is a source of bias. Another limitation was the different definitions used for complications after IFL. An attempt should be made to standardize the definitions used for postoperative wound complications in vulvar cancer patients for this will improve the comparability between published studies in the future.

5. Five year view

Even though new surgical modifications were implemented, the complication rate after IFL in vulvar cancer patients remains high. In the near future, more research is expected to further reduce this morbidity. Besides research on reducing the complications after IFL, research will focus on new treatment regimens in order to limit the indication for IFL. Reducing the number of patients with an indication for IFL can be achieved by the introduction of a repeat SN procedure and/or radiotherapy on the groin. However, it should be kept in mind that the consequences of a groin recurrence are significant, with a 5-year survival rate of only 0–15% [51–53]. Therefore, determination of the lymph node status remains an important part in the treatment of vulvar cancer patients.

The safety of a SN procedure in patients with a local recurrence of vulvar SCC has not been proven yet [54]. As a consequence, patients with a local recurrence after an earlier negative SN do not perceive the benefits of the SN procedure in terms of the omission of an IFL. Research concerning the safety of a (repeat) SN procedure instead of an IFL in patients with recurrent vulvar SCC is expected within the upcoming years.

In 2018, results will be expected of the GROINSS-VII study that will provide more information on the safety and efficacy of radiotherapy instead of IFL in patients with micro-metastases in the sentinel lymph nodes.

Replacement of IFL by other treatment options with less treatment-related morbidity but the same effectiveness and safety will be a step forward in treating vulvar SCC patients. For patients who still have an indication for IFL, research is expected on minimally invasive techniques for IFL to determine the oncologic safety and the benefits in terms of reduced postoperative morbidity. Furthermore, the device used during surgery may be a key factor in preventing postoperative complications. Peri- and postoperative care may also play an important role and also affect the postoperative

complication rates. More prospective studies regarding the peri-and postoperative care should be performed.

Key issues

- Inguinofemoral lymphadenectomy (IFL) is a part of the treatment for approximately half of the patients with primary or recurrent vulvar squamous cell carcinoma.
- IFL in vulvar cancer patients is associated with post-operative groin wound complications such as wound infection, wound breakdown, lymphocele, lymphedema and cellulitis or erysipelas in up to 85% of the patients.
- This review is an up to date summary of surgical techniques and peri- and postoperative care protocols that have been studied to reduce this morbidity
- Surgical techniques such as separate incisions for IFL, unilateral IFL, sparing of the saphenous vein, preservation of the fascia lata and continuous skin suture do reduce the postoperative complications.
- Peri- and postoperative care is described in a few publications; it remains unclear if peri-operative prophylactic anticoagulation or antibiotics influences the number of postoperative complications. The use of post-operative prophylactic compression garments does not reduce post-operative complications. There is no consensus on the optimal duration of drainage of the groin in order to prevent postoperative complications.
- After the implementation of several new surgical techniques, the morbidity after IFL decreased but remains high and clinically meaningful.
- More research is needed on surgical techniques and peri-or postoperative care to further reduce the complication rates after IFL in vulvar cancer patients.

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Declaration of interest

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